Research priorities for triazole-resistant *A. fumigatus* (environmental route) and triazole fungicides in the United States

1) Expand current knowledge of the epidemiology of triazole-resistant *A. fumigatus* colonization and infections in United States: by specific patient populations, regions, and over time

- What is the burden of triazole-resistant *A. fumigatus* infections in patients?
    - Describe the healthcare utilization patterns and outcomes for patients involving triazole-resistant *A. fumigatus* species?

- What are risk factors for patient acquisition of triazole-resistant *A. fumigatus* colonization and infections?

- What are the trends in resistance phenotypes and genotypes in patients?

    - Would try to get at above questions using surveillance data (CDC's Emerging Infections Program [EIP], Antimicrobial Resistance Laboratory Network [ARLN]), large administrative datasets (e.g., MarketScan, IQVIA), electronic medical record datasets

2) Strengthen knowledge on the distribution of triazole-resistant *A. fumigatus* in the environment and the link to disease in patients in the United States

- What factors are associated with increased prevalence of these organisms in the environment (e.g., region, climate, fungicide use, other agricultural/composting practices, crop type)?

- How common are triazole-resistant *A. fumigatus* species in the environment?
    - Could we conduct strategic sampling in agricultural and non-agricultural areas to assess the geographical boundaries of *A. fumigatus* resistance? Utility of air/wastewater surveillance for monitoring the prevalence of azole resistance in the environment?

- Trends in resistance phenotypes, genotypes, or TR34/TR46 markers by PCR in the environment?

- In the United States, where are hotspots for the selection of triazole-resistant *A. fumigatus*?
    - *Hotspots might be defined as sites that support the growth, reproduction, and genetic variation of A. fumigatus and contain residues of azole fungicides would facilitate the emergence, amplification, and spread of triazole-resistance mutations (Schoustra et al, EID 2019).*

- Characterize the dynamics of release of *A. fumigatus* from a hotspot and transmission to patients.
    - Could we design a study focused on quantification of aerial dispersal of *A. fumigatus* conidia from hotspots and investigate occupational exposure of agricultural workers to azole-resistant *A. fumigatus*?

- What are the dynamics of competition between resistant and wild-type strains in these environments that contain low amounts of azoles? Do azole resistant isolates have an evolutionary advantage over susceptible strains when growing in soil contaminated with azoles?
    - Answering this question will help to clarify the role of fungicides in selection for azole resistance and rule out the hypothesis that other factors in the environment might have caused the emergence of azole resistance

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3) Evaluate strategies to reduce the impact of triazole fungicide use on promotion of triazole-resistant *A. fumigatus* in the environment and ultimately in humans

- What are the most effective strategies to reduce the quantity of triazole fungicides used or their impact on promoting triazole-resistance in *A. fumigatus*
    - Examples of potential strategies to evaluate include combining triazoles with biochemical agents, using non-triazole fungicides, use of hemp-based adsorbents, biocontrol agents, aerobic composting, other forms of integrated pest management. Consider strategies used in other countries.
    - What would be the economic impact and acceptability among partners of various strategies to reduce the quantity of fungicide use or reduce their impact on promoting triazole-resistance among *A. fumigatus*?

- Are certain DMI types and uses more prone to select for triazole resistance in *A. fumigatus*? What are DMI half-lives in specific environments under different conditions? Association between environmental persistence of DMIs and promotion of resistance?

- What are the relative impacts of medicinal, agricultural, and other (e.g., materials) uses of triazole compounds on the promotion of triazole-resistant A. fumigatus in the environment and ultimately in patients?